Pharmacologic Therapies for Glucose Management

- ❖ Medication therapy can involve oral agents, insulin, or a combination of the two therapies, and is an integral component of blood sugar control in conjunction with diet and exercise.
- ❖ Medication therapy is a therapeutic tool for use in lowering and maintaining blood glucose levels.

Why is medication therapy used?

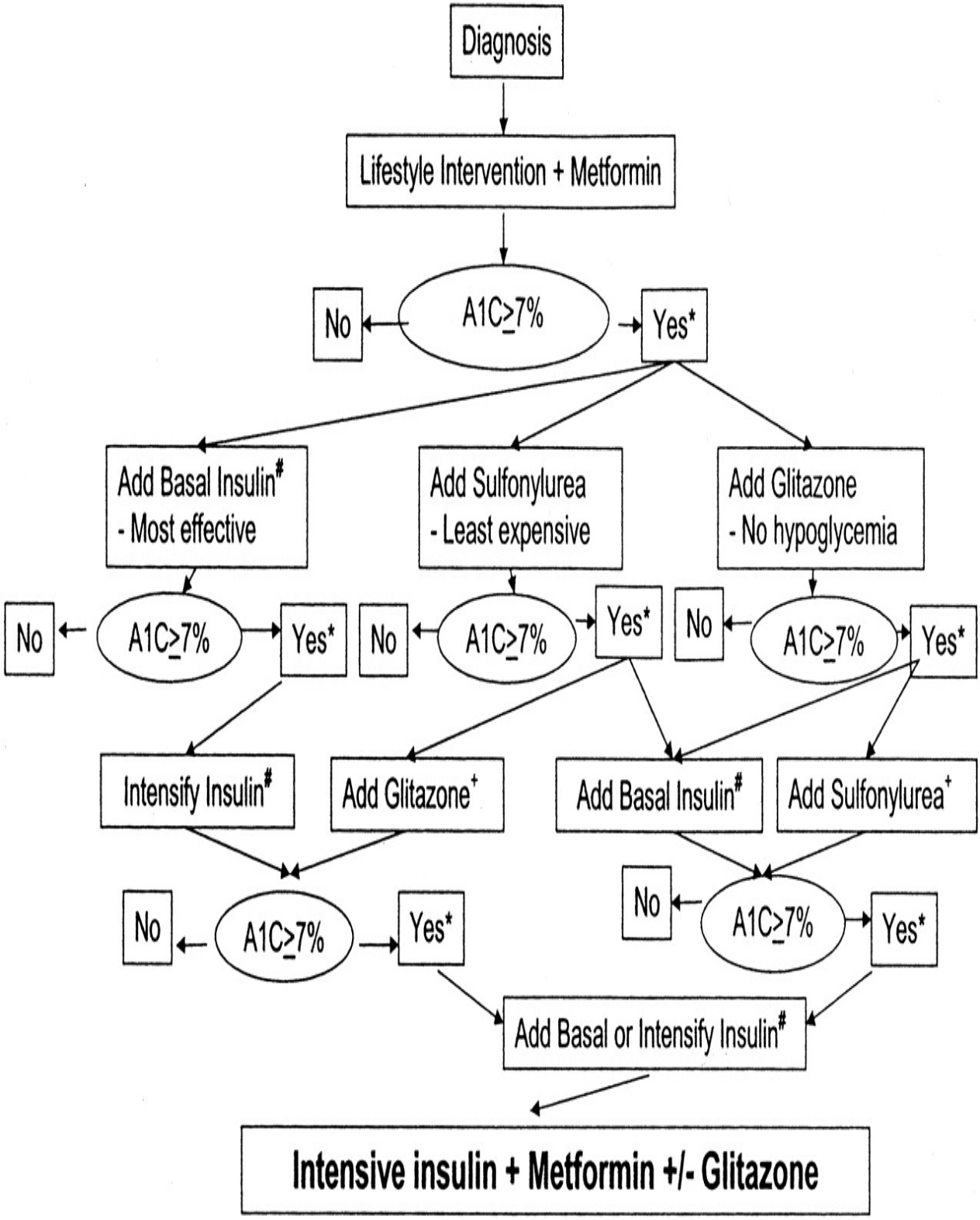
Results from the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complication Trial (DCCT) conclusively revealed that lowering blood glucose reduces the risk of developing complications. Medication therapy is a potential therapeutic tool for use in accomplishing blood glucose goals when used in conjunction with diet and exercise.

Using medication/insulin therapy in practice.

- ❖ Weight gain can occur with insulin therapy in addition to some oral agents. (Insulin Detemir is an exception.)
- ❖ The use of insulin secretagogues and insulin can pose the risk of hypoglycemia.
  1. This risk must be taken to achieve improved glycemic control; however, in some patients, such as the elderly, the risks may outweigh the benefits.
  2. Self-monitoring of blood sugars allows for better adjustment of therapy as well as better recognition and treatment of hypoglycemia.
  3. Ongoing communication between the patient and the diabetes care team is critical to reach glycemic goals.
  4. Diabetes education informs the patient about the interplay between medications, carbohydrate intake, exercise, stress, and illness. This allows for better glycemic control.
- ❖ Insulins glargine (Lantus) and detemir (Levemir) are basal insulins with 24-hour duration. In a randomized double blind study conducted by Heise et al (2004), comparing the glucose lowering effects of insulin detemir, glargine, and NPH in people with type 1 diabetes, results suggest that insulin detemir has a significantly more predictable glucose lowering effect than both NPH insulin and insulin glargine.
- ❖ Lente and Ultra Lente insulins have been taken off the market. Refer to the Eli Lilly website for additional information. http://www.lilly.com/products/index.html
- ❖ Insulin action (absorption and duration) may be variable for different people.
- ❖ The mixing of appropriate insulins and/or multiple daily injections can improve blood glucose levels. (Refer to section on intensive insulin therapy on page 51.)
- ❖ As a general rule, the mixed insulins should be of the same brand.
- ❖ Regular or analog (Lispro, aspart, and glulisine) insulins should be drawn up before the longer acting insulins to prevent contamination of the faster acting insulin, leading to dose variance. Detemir and glargine should not be diluted or mixed with any other insulin preparations or solutions.
- ❖ Refer to the chapter on gestational diabetes for indications during pregnancy.
- ❖ Care should be taken to not confuse clear insulins such as glargine and detemir with rapid acting insulins. Please refer to the table on page 48 for additional information on insulin.
- ❖ Refer to Figure 2 on the following page for the current algorithm for metabolic management of type 2 diabetes (Nathan et al, 2006).

Figure 2: Algorithm for the Metabolic Management of Type 2 Diabetes

Nathan, D., Buse, J., Davidson, M., Heine, R., Holman, R., Sherwin, R., & Zinman, B. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy**. Copyright © 2006 American Diabetes Association. From *Diabetes Care,* Vol. 29, 2006; 1963-1972. Reprinted with permission from *The American Diabetes Association*.**



Overview of Current Pharmacologic Therapies for Glucose Management

Medication	Action	Prescribing Considerations
BIGUANIDES		
Metformin (Glucophage & Glucophage XR, Riomet, and Glumetza)	*Decreases gluconeogenesis, enhances insulin sensitivity by increasing peripheral glucose uptake and utilization.* Refer to packaging label for additional prescribing considerations	• Metformin combined with lifestyle intervention should be initiated in newly diagnosed type 2 diabetes. Refer to http://dave.md/s/indexp.cfm?aid=998 • Start at low dose, titrate up • GI symptoms: diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia most common side effects; these symptoms are generally transient and resolve spontaneously during continued treatment; taking with food and/or temporarily reducing the dose may be helpful • May have positive effects on triglycerides, total cholesterol, and LDL Contraindicated in: ▪ men with serum creatinine 1.5 or greater, and in females with 1.4 or greater ▪ hepatic dysfunction and should not be used in patients with excessive alcohol use ▪ acute or chronic lactic acidosis ▪ may be contraindicated in patients with CHF ▪ use > 80 years of age unless creatinine clearance is normal • Generally not indicated during pregnancy, breastfeeding, or in children under 10 years of age; Glucophage XR indicated for use ≥ 17 years of age or older • Should be temporarily withheld in situations of cardiovascular collapse, acute MI, acute exacerbation of CHF, use of iodinated contrast media, and a major surgical procedure • Requires 2-11 weeks of use before determining effectiveness

Medication	Action	Prescribing Considerations
THIAZOLIDINEDIONES (GLITAZONES)		

Medication Action Prescribing Considerations for THIAZOLIDINEDIONES (GLITAZONES)

The FDA's review of rosiglitazone's possible increased risk of cardiovascular events is ongoing. Until further data is available, this drug now carries a "Black Box" warning from the FDA advising patients and physicians to be aware of signs of heart failure. Risk versus benefits regarding use of this drug should be evaluated on a case-by-case basis, with mutual decision-making between the physician and patient (Nissen, 2007). Black Box warning further indicates that thiazolidinediones are "not recommended in patients with symptomatic heart failure" (Avandia and Actos Product Information).

Rosiglitazone has additional information in the "Black Box" warning regarding cardiac ischemia. A review of 42 studies (primarily comparing Rosiglitazone to placebo) found an increase in the occurrence of myocardial ischemic events. However, three studies comparing Rosiglitazone to other oral agents to treat diabetes have not yielded definitive results (Avandia Product Information).

Rosiglitazone (Avandia) **Pioglitazone (Actos)**	*Improves insulin sensitivity within peripheral muscle and adipose sites; Inhibits hepatic gluconeogenesis.*	• Requires 2-16 weeks of use before determining effectiveness • Liver enzymes should be checked prior to initiation of therapy with Rosiglitazone and periodically thereafter per clinical judgment of the healthcare provider • Rosiglitazone may increase HDL and LDL • Pioglitazone decreases triglycerides and increases HDL • May cause weight gain and fluid retention • Use with caution in patients with hepatic disease or with advanced heart disease • Generally not indicated during pregnancy, breastfeeding, or in children • Decreases oral contraception effectiveness and may cause resumption of ovulation in anovulatory women

Medication	Action	Prescribing Considerations
ALPHA-GLUCOSIDASE INHIBITORS		
Acarbose (Precose) **Miglitol (Glyset)**	*Delays digestion of carbohydrates, lowers rise in post-meal blood glucose.*	• To be taken with first bite of food • GI symptoms are the most common reaction; the incidence of diarrhea and abdominal pain tend to diminish with continued treatment • Reduces bioavailability of Digoxin, Propanolol, Ranitidine, digestive enzymes • Avoid use in patients with GI disorders • Avoid use of Acarbose in patients with cirrhosis • Neither agent recommended in patients with creatinine clearance < 25 mL/min • Generally not indicated during pregnancy, breastfeeding, or in children • Must use dextrose (not sucrose) to correct hypoglycemia when taking Acarbose • Refer to packaging label for additional prescribing considerations
OTHERS		
Glucovance	*Combination of Glyburide and Metformin*	• See Glyburide and Metformin
Metaglip	*Combination of Glipizide and Metformin*	• See Glyburide and Metformin
Avandamet	*Combination of Rosiglitazone and Metformin*	• See Rosiglitazone and Metformin
Actos + Met	*Combination of Pioglitazone and Metformin*	• See Pioglitazone and Metformin
Janumet	*Combination of Januvia and Metformin*	• See Januvia and Metformin
Avandaryl	*Avandia plus Glimepiride*	• See Avandia and Glimepiride

Medication	Action	Length of Action	Prescribing Considerations
SULFONYLUREAS			
Chlorpropamide (Diabinese)	*Stimulates insulin release from the pancreas.*	72 hours	• Hypoglycemia, gastrointestinal complaints and weight gain are most common side effects • Contraindicated in patients with diabetic ketoacidosis, severe infection, surgery, or trauma • Avoid use in patients with significant alcohol consumption • Generally not indicated during pregnancy, breastfeeding, or in children • Refer to packaging label for additional prescribing considerations
Tolazamide (Tolinase)		10-14 hours	
Tolbutamide (Orinase)		6-12 hours	
Glyburide (Diabeta) (Micronase) (Glynase)		12-24 hours	
Glipizide (Glucotrol) (Glucotrol XL)		12- 16 hours	
Glimepiride (Amaryl)		24 hours	
Medication	**Action**	**Length of Action**	**Prescribing Considerations**
MEGLITINIDES			
Repaglinide (Prandin)	*Stimulates insulin release from the pancreas. Insulin release is glucose dependent and diminishes at low glucose concentrations.*	2-3 hours	• Administer 15 to 30 minutes before meals • Only works in the presence of glucose • Approved for combination use with Metformin and Thiazolidinediones • Use Repaglinide cautiously in patients with hepatic impairment • Repaglinide contraindicated in patients with diabetic ketoacidosis • Severe infection, surgery, or trauma • Generally not indicated during pregnancy, breastfeeding, or in children • Refer to packaging label for additional prescribing considerations
Nateglinide (Starlix)		4 hours	

Medication	Action	Prescribing Considerations
INCRETIN MIMETIC INJECTION-SYNTHETIC PEPTIDE		
Exenatide (Byetta)	*Onset of action is unknown. Time of peak is 2.1 hours. Indicated as adjunctive therapy to improve glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.* *It enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.*	• Common side effects include mild nausea, vomiting, diarrhea, jittery feeling, dizziness, headache, and dyspepsia • Contraindicated in patients with long-standing gastroparesis and end-stage renal disease • May reduce appetite and cause weight loss • Acute pancreatitis has been noted in 30 case reports; patients at risk include those with gallstones, extremely high triglycerides, or increased alcohol consumption; watch for severe abdominal pain • Given subcutaneously; packaged in injectable pre-filled pens • Store new, unused Byetta Pens in the refrigerator. DO NOT FREEZE. After first use, keep pen at room temperature not to exceed 77 degrees F. for up to 30 days; throw pen away after 30 days even if not completely used • Administer BID within 60 minutes before morning and evening meals • Refer to packaging label for additional prescribing considerations

Sitagliptin phosphate (Januvia) **Available in 25, 50, and 100 mg tablets** **Creatinine Clearance:** **>50cc/min=100mg/day** **<50cc/min but>30cc/min=50mg/day** **<30cc/min=25mg/day** **DPP-4 inhibitor** **(slows inactivation of incretion hormones)**	*Indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR agonist (e.g. thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control. Not indicated for patients with type 1 DM or to treat diabetes ketoacidosis.* • *Improves insulin secretion* • *Decreases glucagon secretion* • *Peak plasma concentrations 1-4 hrs* • *Drug half-life is 12 hrs*	• **Common side effects** are: upper respiratory infection, nasopharyngitis, and headache • Administer BID within 60 minutes before morning and evening meals • Contraindicated in patients with long-standing gastroparesis and end-stage renal disease • May reduce appetite and cause weight loss • Acute pancreatitis has been noted in 30 case reports; patients at risk include those with gallstones, extremely high triglycerides, or high alcohol use; watch for severe abdominal pain • **Precautions:** Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD; assess renal function prior to initiation of drug • When used with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce risk of hypoglycemia • Serious allergic and hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions such as Stevens-Johnson Syndrome have been associated with Januvia; promptly stop the drug, assess, monitor, and initiate alternate treatment for diabetes • Not indicated for use in children under 18 years of age, pregnancy, or with lactation • Refer to packaging label for additional prescribing considerations

Medication	Action	Prescribing Considerations
SYNTHETIC HUMAN AMYLIN ANALOG		
(Pramlintide) Symlin	*Onset of action is unknown. Drug half-life is 48 minutes.* *Mimics 3 important actions of Amylin that impact glucose appearance:* 1. *Inhibits inappropriately high postprandial glucagon secretion* 2. *Slows gastric emptying* 3. *Promotes satiety and reduces caloric intake, decreases appetite, promotes weight loss*	• Given as a sub-Q injection • Do not mix with insulin – separate injection sites by at least 2 inches • Use U-100 insulin syringe • Inject before each major meal • Can be used as an adjunct treatment in patients with type 1 or type 2 DM who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without concurrent sulfonylurea agent and/or metformin • Warning: Pramlintide acetate is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. • Generally not indicated during pregnancy, breastfeeding, or in children • Refer to package insert for additional prescribing considerations

How do the insulins compare with one another?

Insulin Type	Onset of Action	Time of Peak	Duration of action
Rapid Acting Analogs			
Aspart (Novolog)	5 - 15 minutes	½ - 1½ hours	3 - 5 hours
Lispro (Humalog)	10 - 15 minutes	½ - 1½ hours	3 - 4 hours
Glulisine (Apidra)	15 - 30 minutes	½ - 1½ hours	3 - 4 hours
Short Acting			
Human Regular	30 - 60 minutes	2 - 4 hours	8 - 12 hours
Intermediate Acting			
Human NPH	1 ½ hours	4 - 12 hours	24 hours
Human Lente	2 - 5 hours	7 - 15 hours	24 hours
Basal			
Glargine (Lantus)	1 ½ hours	peakless	24 hours*
Detemir (Levemir)	0.8 - 2.0 hours	relatively flat	up to 24 hours* *DO NOT MIX with other insulin
Lente and Ultra Lente			
Lente and Ultra Lente insulins have been taken off the market. Refer to the Eli Lilly website for additional information. http://www.lilly.com/products/index.html			
Pre-Mixed			
Humalog Mix 75/25 (NPH/Lispro)	10 minutes	½ - 4 hours	24 hours
Human 70/30 (NPH/R)	10 minutes	2 - 12 hours	24 hours
Human 50/50 (NPH/R)	30 minutes	1 - 6 hours	14 hours
Novolog 70/30	10 minutes	2 - 12 hours	24 hours

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